Paper No. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEPHEN O'GORMAN and GEOFFREY WAHL

Appeal No. 2003-1127
Application No. 08/919,501

HEARD: February 3, 2003

Before WINTERS, SCHEINER and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51, all the claims remaining in the application.

Claims 12, 26, 40 and 44 are representative of the subject matter on appeal and read as follows:

12. Non-human mammalian embryonic stem cells containing a nucleic acid construct comprising a mammalian germline-specific promoter operatively associated with a recombinase coding sequence, wherein the nucleic acid construct is in the genome of the stem cells and wherein the recombinase is not expressed in the stem cells in cell culture.

26. Non-human mammalian embryonic stem cells comprising a germline-specific promoter operatively associated with a recombinase coding sequence and a transcriptionally active selectable marker flanked by two recombinase recombination target sites in the genome of the stem cells.

40. A method for the production of recombinant alleles, said method comprising:

introducing at least one nucleic acid construct into the genome of mammalian embryonic stem cells,

wherein said at least one nucleic acid construct comprises a germline-specific promoter operatively associated with a recombinase coding sequence, a nucleic acid fragment flanked by a first pair of recombination target sites and a selectable marker flanked by a second pair of recombination target sites and a selectable marker flanked by a second pair of recombination target sites,

passaging the genome derived from embryonic stem cells selected for expression of the marker through gametogenesis to obtain a transformed gamete; and

crossing the genome of the transformed gamete with the genome of a wild type animal, thereby obtaining first generation progeny wherein the marker is excised in the germline.

44. A method for the generation of recombinant non-human animal, said method comprising:

combining a nucleic acid construct comprising a germline-specific promoter operatively associated with a recombinase coding sequence with host pluripotential ES cells derived from early preimplantation embryos,

introducing these embryos into a host female, and

allowing the derived embryos to come to term such that a recombinant non-human animal is thereby produced by operation of the recombinase upon passage of the genome derived from the embryonic stem cells through gametogenesis.

The examiner relies on the following references as evidence of non-enablement:

L.J. Mullins and J.J. Mullins (Mullins), "Perspective Series: Molecular Medicine in Genetically Engineered Animals," J. Clin. Invest., Vol. 98, No. 11, pp. S37-S40 (Supplement 1996)

Lewandoski et al. (Lewandoski), "*Zp3-cre*, a Transgenic Mouse Line for the Activation or Inactivation of *loxP*-Flanked Target Genes Specifically in the Female Germ Line," Current Biology, Vol. 7, pp. 148-151 (1997)

Wall et al. (Wall), "Transgenic Dairy Cattle: Genetic Engineering on a Large Scale," J. Dairy Sci., Vol. 80, pp. 2213-2224 (1997)

Claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51 stand rejected under 35 U.S.C. § 112, first paragraph, as "[t]he specification does not enable any person skilled in the art . . . to make and/or use the invention commensurate in scope with the claims" (Brief, page 7). Claims 28-32, 34-44 and 46-51 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

BACKGROUND

"[T]he present invention relates to methods for producing embryonic stem [(ES)] cells bearing nucleic acid sequences that have been rearranged by a site-specific recombinase expressed from a construct controlled by a . . . germline-specific promoter[.]" Specification, page 1.

DISCUSSION

Enablement

According to the examiner (Answer, page 7)

> [T]he specification, while being enabling for a mouse ES cell whose genome comprises a nucleic acid sequence encoding recombinase operatively linked to the MP1 promoter, and a method of making a transgenic mouse comprising implanting said mouse ES cells into a host female such that a transgenic mouse is obtained, wherein spermatid of said transgenic mouse express said recombinase, does not reasonably provide enablement for making and/or using any ES cell comprising DNA encoding recombinase operably linked to any germline-specific promoter as broadly claimed, making any transgenic animal or making any recombinant allele as broadly claimed.

A specification which describes "making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). In other words, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this

includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Thus, the threshold issue here is not whether appellants have established that their disclosure is broadly enabling for the scope of the claims, rather, the issue is whether the PTO has met its "initial burden of setting forth a reasonable explanation as to why" it is not. Keeping this in mind, we have considered the specific issues raised by the examiner in support of his position, but find that they provide insufficient reason for "doubting any assertions in the specification as to the scope of enablement."

The examiner notes that "[t]he ES cells recited in the claims require DNA encoding recombinase operably linked to a 'germline-specific promoter'," and concludes that "therefore, . . . the ES cells must provide germline transmission of the transgene" (Answer, page 8). Inasmuch as Mullins teaches that "[t]he culture conditions required to maintain cells that provide pluripotency and are capable of germline transmission are dependent upon the species of cells" and "that ES cells providing germline transmission were only available in mice," the examiner believes that "[t]he specification does not enable making and/or using any non-human mammalian ES cells . . . as broadly required in the claims" (id.).

If we understand the examiner's concern, it is that stable germline transmission of a transgene to the offspring of chimeric mammals other than mice may be less predictable than germline transmission in mice. Nevertheless, as appellants point out, the rejection was applied to all of the pending claims "without considering each of the claims independently" (Reply Brief, page 5). With respect to most of the claims on

appeal, appellants make a compelling argument, uncontroverted by the examiner, that "there is in fact[,] no requirement for 'germline transmission'" (Reply Brief, page 5).

By way of example, appellants point out that "[c]laims 12-15, 18-24, 26 and 49-51 are directed to ES cells . . . modified (e.g., transfected) to contain a nucleic acid construct comprising a recombinase," and "[t]his is all that is required by [these] claims" (id.). Since "Mullins clearly states that ES cells are obtainable from a variety of species" and "methods of producing ES cells containing additional nucleic acid constructs were clearly known . . . at the time of filing," appellants argue that the specification is broadly enabling for making and using non-human mammalian ES cells containing the required promoter-recombinase constructs.

Similarly, appellants point out that claims 28-32 and 34 are "directed to excision of a target marker in [non-human] ES cells also expressing recombinase . . . [by] introducing two constructs into ES cells, and developing the ES cells through gametogenesis, at which time-point the recombinase becomes expressed." Appellants maintain that this "requires only germline expression of recombinase in the resulting chimeric animal, and [again] . . . there is no requirement for 'germline transmission' to future generations" (Reply Brief, pages 5-6). Since Mullins teaches that "pluripotent rat, sheep and cattle ES cells capable of producing chimeric offspring have been reported" (Brief, page 13), appellants argue that the specification "clearly enables one of skill in the art to make and use any mammalian ES cell as claimed" (id.).

Certain of the claims do appear to require transmission of a transgene to the offspring of a chimeric animal and a wild-type animal, but are limited to rodents (e.g.,

claims 35-39), so this aspect of the examiner's rejection would not appear to be relevant here either. With respect to any remaining claims, not limited to rodents, which may require transmission to offspring of a chimeric animal, we can only say that the examiner has not begun to provide an adequate or reasonable factual basis for doubting any assertions in the specification as to the scope of enablement.[1]

The examiner also believes that "the specification does not enable any 'germline-specific' promoters as claimed" (Answer, page 9). The examiner notes that "the specification contemplates using 'germline-specific promoters' such as the MP1," but argues that MP1 "also causes expression in cells other than germ cells . . . [and] [t]herefore is not specific to the germline as claimed" (id.). According to the examiner, the specification "does not provide adequate guidance indicating that the protamine 2, c-kit, ZP1, ZP2 or ZP3 promoters are specific to only germ cells" either (id.).

We agree with appellants that "the [e]xaminer's position cannot be reconciled with the state of the art, wherein MP1 is widely accepted by those of skill in the art to be a germline-specific promoter" (Brief, page 16), as, for that matter, are all the other

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[1] "The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original).

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

promoters listed in the specification. There are a number of references of record (see e.g., page 6 of the specification), establishing that those of skill in the art, at the time of the invention, considered the MP1, protamine 2 and c-kit promoters to be spermatid-specific, and the ZP1, ZP2 and ZP3 promoters to be oocyte-specific, despite background levels of expression in other tissues. Moreover, the examiner's position on this matter is inconsistent with his acknowledgment that the specification is "enabling for a mouse ES cell whose genome comprises a nucleic acid sequence encoding recombinase operatively linked to the MP1 promoter" (Answer, page 7).

Finally, the examiner argues that "obtain[ing] germline-specific recombinase activity that is sufficient to mediate excision of DNA flanked by recombination sites using transgenic animals" is unpredictable, apparently "because of the variability of transgene expression" and because "the physiological result of such expression in livestock was not always accurately predicted in transgenic mice" (Answer, page 9). If we understand the examiner's concern here, it is that transgenic offspring may not exhibit recombinase activity, and that phenotypic changes may not always be detectable or predictable in transgenic offspring. Again, the examiner has not explained the relevance of these concerns to the claimed invention. It does not appear that any of the claims, even those that require the presence of a transgene in transgenic offspring, require recombinase activity in the transgenic offspring. With respect to the phenotype of the offspring, we agree with appellants that "there is no requirement in the present methods for generating an outwardly manifesting phenotype," and "a recombinant allele or a transgenic animal is created upon incorporation of foreign DNA, whether or not any outward phenotype is manifested" (Brief, pages 17-18).

Having carefully considered the record as a whole, we find that examiner has not established that the specification fails to satisfy the enablement requirement of the first paragraph of 35 U.S.C. § 112. Accordingly, the rejection of claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51 under the first paragraph of 35 U.S.C. § 112 is reversed.

Indefiniteness

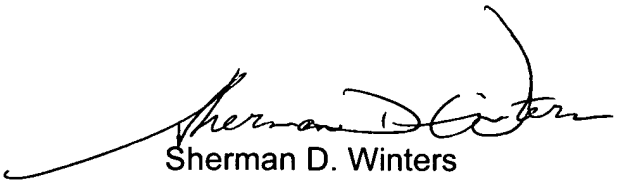
Claims 28-32, 34-44 and 46-51 stand rejected under the second paragraph of 35 U.S.C. § 112. See the Answer, pages 12-13. We have carefully reviewed the examiner's criticisms of the claims, but we find that the examiner's comments reflect a strained reading of the claims. The test for definiteness is simply whether one skilled in the art would understand the language of the claims when the claims are read in light of the specification. See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Having reviewed the claims in light of the specification, we are not persuaded that one skilled in the art would have any difficulty in interpreting the claims.

Accordingly, the rejection of the claims under the second paragraph of 35 U.S.C. § 112 is reversed.

SUMMARY

In our view, the examiner has not established that the claims are not enabled throughout their scope, or that the claims are indefinite. The rejections of the claims under the first and second paragraphs of 35 U.S.C. § 112 are reversed.

REVERSED



Sherman D. Winters)
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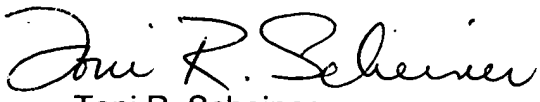
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